

Modeling Concentration Profiles of Infliximab in Colon Wall to Ensure Efficacy of Drug-Eluting Biodegradable Stent in the Management of Crohn's Disease

BEE 4530

Computer-Aided Engineering: Application to Biomedical Processes

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1. Executive Summary

Crohn's disease (CD) is a chronic inflammatory disorder of the bowel affecting more than 500,000 people in the US. Current delivery mechanisms for CD medications lack site and time specificity. Advances in biomaterials have led researchers to look into biodegradable drug-eluting stent as a potential vehicle to overcome the aforementioned shortcomings of current treatments. In order to determine if such a treatment is feasible, we present a model for drug diffusion from a biodegradable with COMSOL 4.3. This model tracks the diffusion of infliximab from the degradable stent into the colon wall with time, as well as the drug degradation in the colon wall. We first compared the diffusion profiles of models with and without stent degradation. We then obtained the average concentration levels in the colon wall and compared it to minimum therapeutic level in literature. We also determined the effect of stent composition on stent degradation velocities. Furthermore, we studied the effect of varying model input parameters on concentration profiles and output parameters. Finally, we validated our model using an analytical solution for drug delivery from a degradable polymer. Our results indicate that stent degradation decreases the average end concentration by 12% to 14%. The average end concentration obtained with the degrading model is $9.923\text{e-}7 \text{ mg/mm}^3$, higher than the minimum therapeutic level, and convergence is reached after 5.3 days. Our model is applicable for a wide range of clinical situations, drug compound choices and polymer choices.

2. Introduction

Crohn's Disease (CD) is a chronic inflammatory disorder of the bowel primarily due to an inappropriate response of the mucosal immune system. It manifests itself through intestinal inflammation that leads to formation of ulcers and progressive tissue damage (Armuzzi, 2008). Over 500,000 people in the US suffer from CD, and its incidence is on the rise in the US and worldwide (Kappelman, 2012). There is no cure to CD. Current medical therapies to manage the disease include salicylates, antibiotics, immunosuppressants, and in the most severe cases of CD, biologics. Infliximab is one such biologic agent; it is a monoclonal antibody against the pro-inflammatory cytokine, TNF- α . However, with the progression of the disease, up to 50% of patients would require a surgical resection of the diseased bowel segment (Dhillon, 2005). Repeated resections eventually lead to shortening of bowel and other complications. Therefore, there is a strong need to steer the course of CD management away from surgical resection and towards a minimally invasive, effective, and sustainable method of management.

Current methods of delivering CD drugs include subcutaneous injection, microcapsule encapsulation, and oral delivery (Akobeng, 2009). Subcutaneous injection and oral delivery are both systematic delivery methods that can cause significant side effects, such as increased risk for infections, jaundice, tuberculosis, and neurological events (Merck, 2013). Microcapsule encapsulation delivers infliximab locally, as it responds to the pH and specific bacterial enzymes in the colon. However, problems such as early release and short transit time limit the applicability of microcapsules. Therefore, there is a clinical need for a more site and time specific CD drug delivery method. Biodegradable drug-eluting stents are a potential vehicle to overcome the aforementioned shortcomings of the current treatments. The stent can be positioned at the affected area, hence the site specificity, and the stent can be designed to elude a set amount of drugs over a specific period of time, hence the time control. The stent is degradable, therefore not requiring removal. Biodegradable stents have been developed for use in the GI tract to overcome strictures and maintain anastomosis (Janik, 2011). A few studies have looked at the possibility of coating the biodegradable stent with anti-inflammatory agent Paclitaxel and placing the stent in the esophagus (Jeon, 2009). However, a drug-eluting biodegradable stent specifically designed to treat CD has not yet been developed. We believe that such a stent can be an innovative and effective alternative therapy for CD. To ensure the effectiveness and safety of such proposal, the diffusion behavior of infliximab from the stent into the colon wall needs to be characterized and extensively studied.

3. Design Objectives

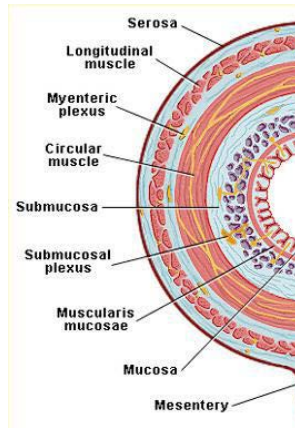
The overall goal of our project is to model the diffusion of infliximab in the colon wall after release from an infliximab-infused biodegradable stent placed in the descending colon. Specifically we seek to accomplish the following five main objectives:

1. Develop a model in COMSOL to simulate diffusion of infliximab into the colon wall and track its subsequent degradation in colon tissue when released from a drug-infused degradable stent placed in the descending colon
2. Compare the diffusion profiles of degrading and non-degrading stent to determine whether stent degradation affects drug diffusion
3. Assess the feasibility of a degradable drug-eluting stent to treat CD by :
 - a. Examining the concentration profiles of infliximab in the colon with time
 - b. Determine the average end concentration of infliximab and compare it to the minimum therapeutic level
 - c. Compare the time of convergence to the time of complete stent degradation
4. Determine the effect of stent composition on stent degradation velocity
5. Through sensitivity analysis, determine the effect of stent strut size, as well as physical and chemical properties, on drug delivery through stent

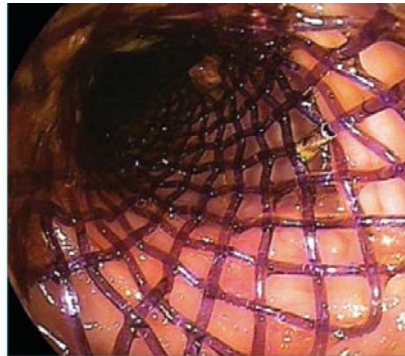
4. Design Schematic

The stent is modeled as a series of circular rings that are in contact with the colon wall without slipping. We modeled the domain as 2D axisymmetric with respect to the lumen center and with respect to the midline of the stent. In 2D, the stent struts are modeled as small disks half-embedded in the colon wall and evenly distributed along the colon wall. The spacing in between the disks represents the pores on the stent.

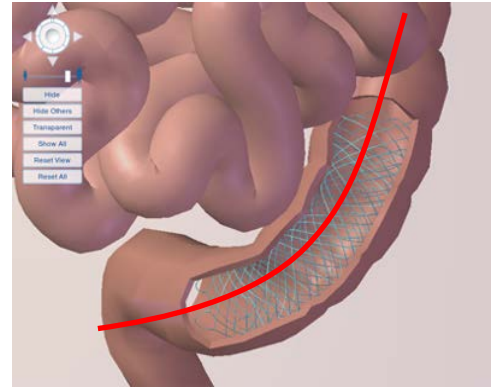
Figure 1a below illustrates the colon anatomy. The colon wall consists of several layers, from serosa on the peritoneal side to mucosa on the luminal side. However, in our simplified model, we modeled the colon as made of one layer of a uniform tissue. Figure 1b is an endoscopic image of a stent deployed in the colon. Figure 1c shows a schematic of a stent deployed in the sigmoid colon. If we cut along the red line in Figure 1c, we are looking at the cross-section of the colon wall, and arriving at our design schematic, Figure 1d. In Figure 1d, the blue area represents the colon wall seen from its cross-section, and the red disks represent the stent struts. The model dimensions are included in the figure. Figure 1f shows a cut-out of the first strut degrading with time. The stent degradation velocity, in other words the rate of stent radius decrease, is given by Eq. 7 in Appendix A. The green borders in Figure 1e represent boundaries with zero flux.



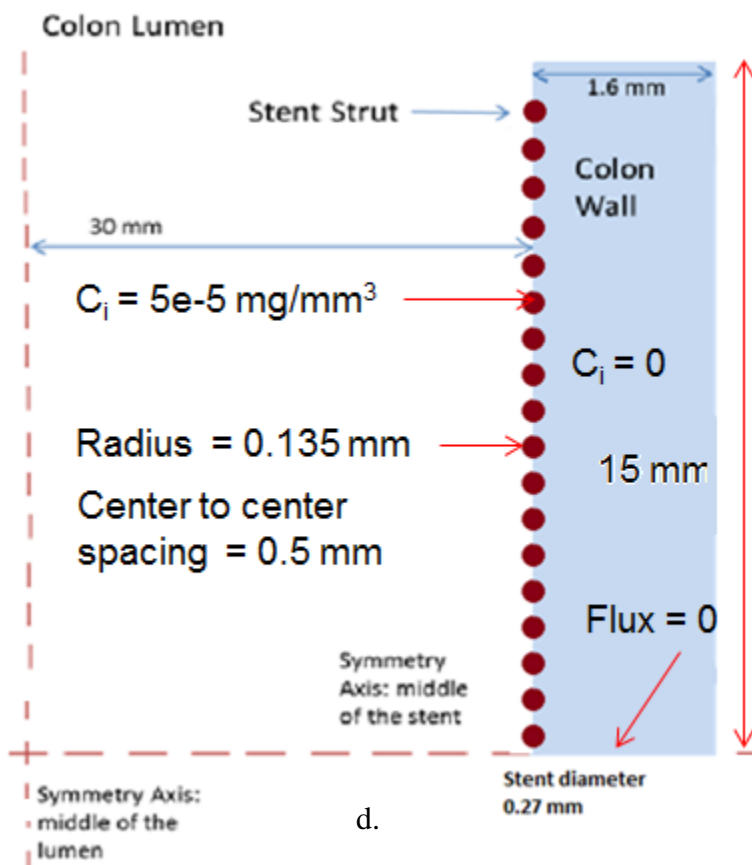
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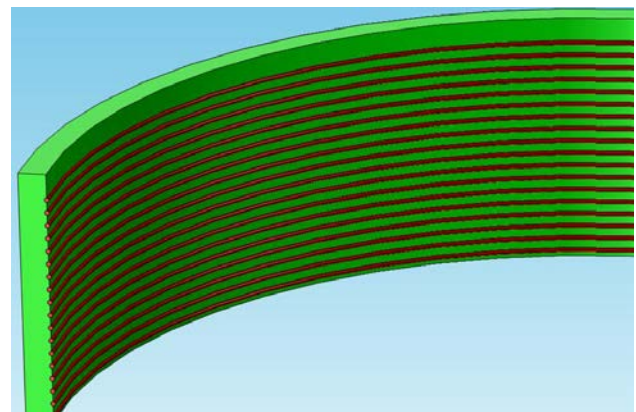
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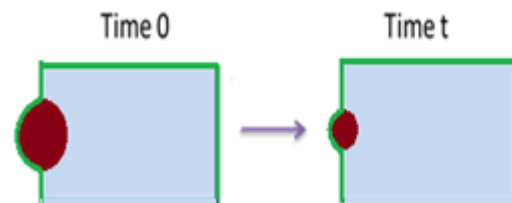
c.



d.



e.



f.

Green: Flux = 0

Figure 1: a. Anatomy of colon wall. The layers are treated as one in our model.
b. Endoscopic image of a stent deployed in the colon. The self-expandable stent half-embeds itself into the colon wall.
c. Computer schematic of stent deployed in the sigmoid colon. A cut along the red line shows the cross-sectional view of our schematic.
d. Schematic of colon-stent domain in our model. The axes of symmetry are with respect to the middle of the lumen and with respect to the midline of the stent. The blue region represents the colon wall, which is 1.6 mm thick and 15 mm long. The

red disks represent the stent struts, which are 0.135 mm in radius and spaced .50 mm apart center to center.

- e. Rotation of the 2D domain with respect to the center of the lumen. The green area represents the colon wall. The stent struts are represented in red.
- f. Cut-out of a schematic of stent degradation. Only the first strut is shown. The strut radius decreases with a velocity given by Eq. 7 in the Appendix A. The green border indicates boundaries of zero flux.

For ease of computation and study feasibility, we make several key assumptions in our study.

1. The colon is assumed to be a regular cylinder that is symmetrical around the central axis. Hence, any heterogeneity in wall layer thickness or characteristics circumferentially is ignored in the present case.
2. Actual colon wall resembles Figure 1a above, with many different types of layers. In order to facilitate the appropriation physical parameters from existing literature, in the present case we simplify the wall to a homogeneous layer.
3. Due to the novelty of our proposed design, there is scarce literature on the relevant physiological data for our input parameters. Therefore, we assume the properties of diseased and healthy tissues to be the same, and the Crohn's lesions to be uniformly distributed.
4. We ignore convective transport of drugs through blood vessels in the colon wall. In reality, as the drug diffuses through the wall, there may be blood vessels nearby that transport drug away from site.
5. We model the stent degradation as occurring through surface erosion. There are two types of degradation behaviors: bulk erosion in which the stent slowly loses consistency while maintaining volume, and surface erosion in which the stent shrinks as it degrades while maintaining density. In the present study, we seek to understand the effect of surface erosion only on drug diffusion.
6. We ignore drug loss to the lumen, as the flow of waste materials in the colon is too complex to model, as opposed to blood flow in the arteries.

5. Results and Discussion

The following section details the results we obtained from the three studies we performed – coupled drug diffusion and stent degradation, diffusion only, and stent degradation only, as they pertain to the specific design objectives listed earlier. We achieved our first objective, which is to develop a COMSOL model to simulate infliximab diffusion and degradation in the colon, when we designed our model.

A. Objective 2: Comparing Degrading Model with Non-Degrading Model

Our second objective is to compare the concentration profiles of the degrading and non-degrading model, and evaluate whether stent degradation affects the diffusion behavior of infliximab. Therefore, in our analysis, we first compared the surface drug concentration plots for the two models to obtain an overall and qualitative understanding of the diffusion behavior.

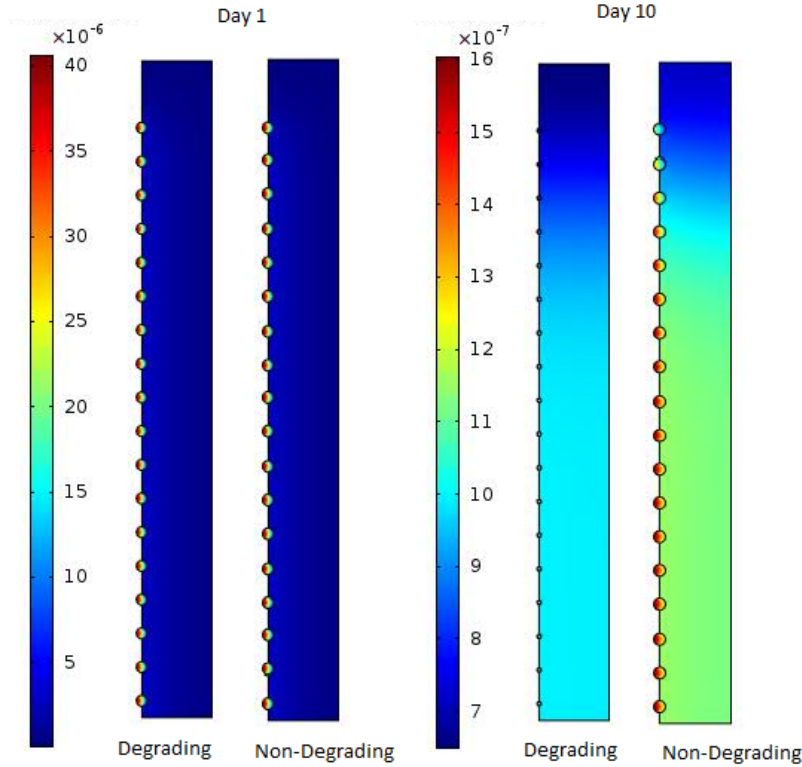


Figure 2: Surface plots of infliximab concentration at two time points for the degrading and non-degrading model. The surface plots of the two models look similar at the end of day 1. At the end of day 10, the surface plot for the non-degrading model shows higher concentration in the colon wall.

Figure 2 above shows the diffusion of infliximab from the stent into the colon wall for both the degrading and the non-degrading models. The surface plot of the degrading model clearly shows the stent struts shrinking with time, while the surface plot of the non-degrading model shows the stent struts remaining the same size for the entire duration of the simulation. In terms of concentration level, the two plots show similar levels at the end of day 1, judge by the coloring. However, at the end of day 10, the plot for the non-degrading model shows higher concentration (light green) compared to the degrading model (light blue). To quantitatively compare the concentration profiles in the

degrading and non-degrading model, we plotted the concentrations of infliximab at different depths with respect to time for both models in Figure 3 below.

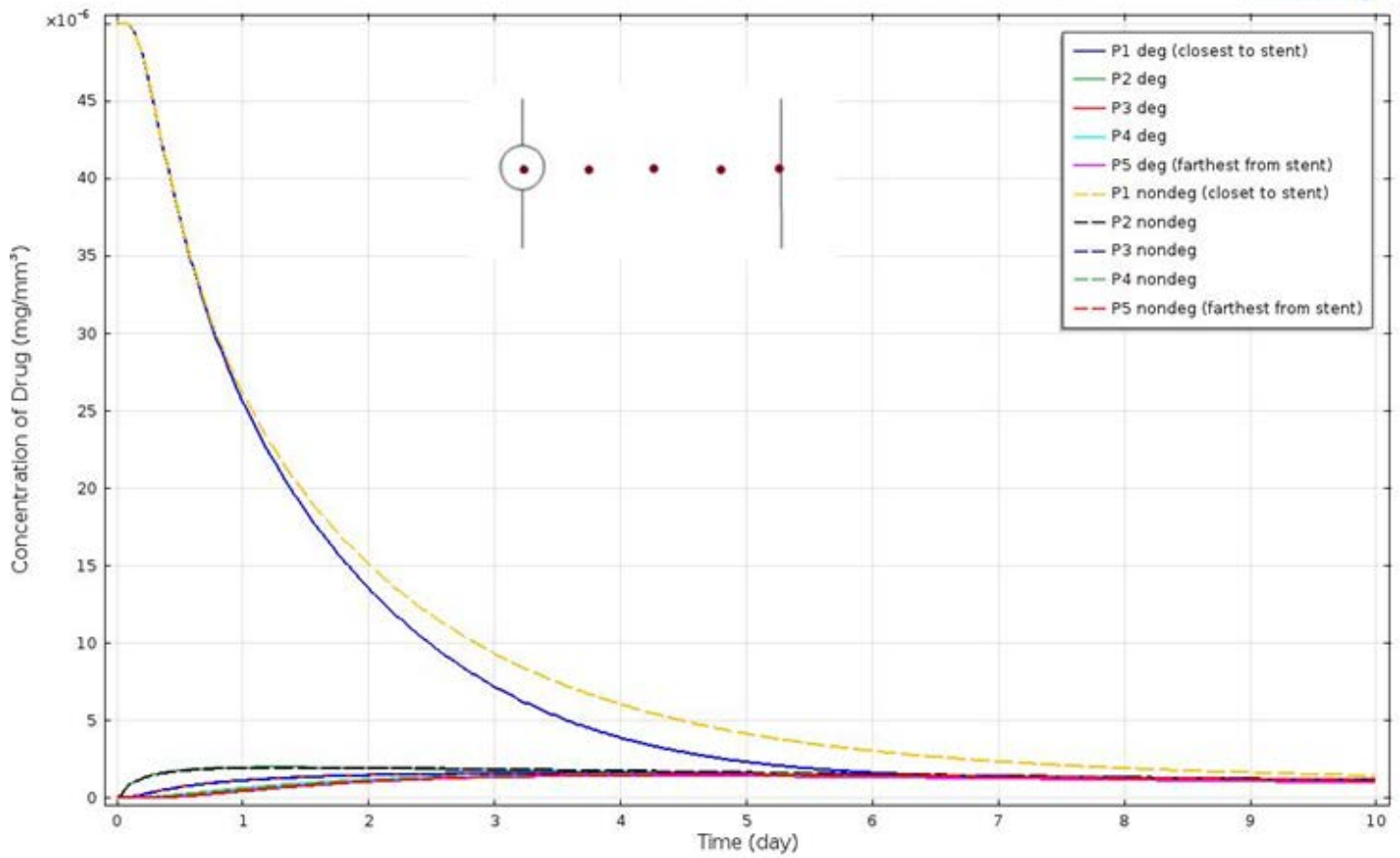


Figure 3: Concentration profiles at different depths in the colon wall for degrading and non-degrading model. The concentration at P1 (point located in the middle of the stent) higher than the concentrations in the colon for both models.

In Figure 3 above, five points uniformly distributed across the colon wall were chosen as points of evaluation. The exact locations of these five points are 6.55 mm above the stent midline, and respectively 30, 30.4, 30.8, 31.2 and 31.6 mm from the center of the lumen. The point located in the stent is termed P1, and the point farthest from the stent is termed P5. The concentrations at P2 to P5 are colon drug concentrations. Figure 3 shows that the drug concentration at the middle of the stent is much higher than the concentrations in the colon at the beginning of the study, which is to be expected, and steadily decreases with time to reach a level that is only slightly higher than the concentrations in the colon. When comparing the concentrations profiles of P2 to P5, we observed that the concentration curves eventually converge, which means that after a certain time period, uniformity in drug concentration is achieved in the colon wall. When comparing the degrading to the non-degrading curves, we observed that the

concentrations at P1 for the non-degrading model are slightly higher than for the degrading model, especially at later times.

To focus more on the concentration profiles in the colon, we replaced P1 with a point that is just outside of the stent strut (6.55 mm above stent midline and 30.14 mm from the lumen). All other points remain the same. This distribution of points allows us to obtain the maximum drug in the colon (the new P1) and visualize the concentration curves in the colon much more clearly.

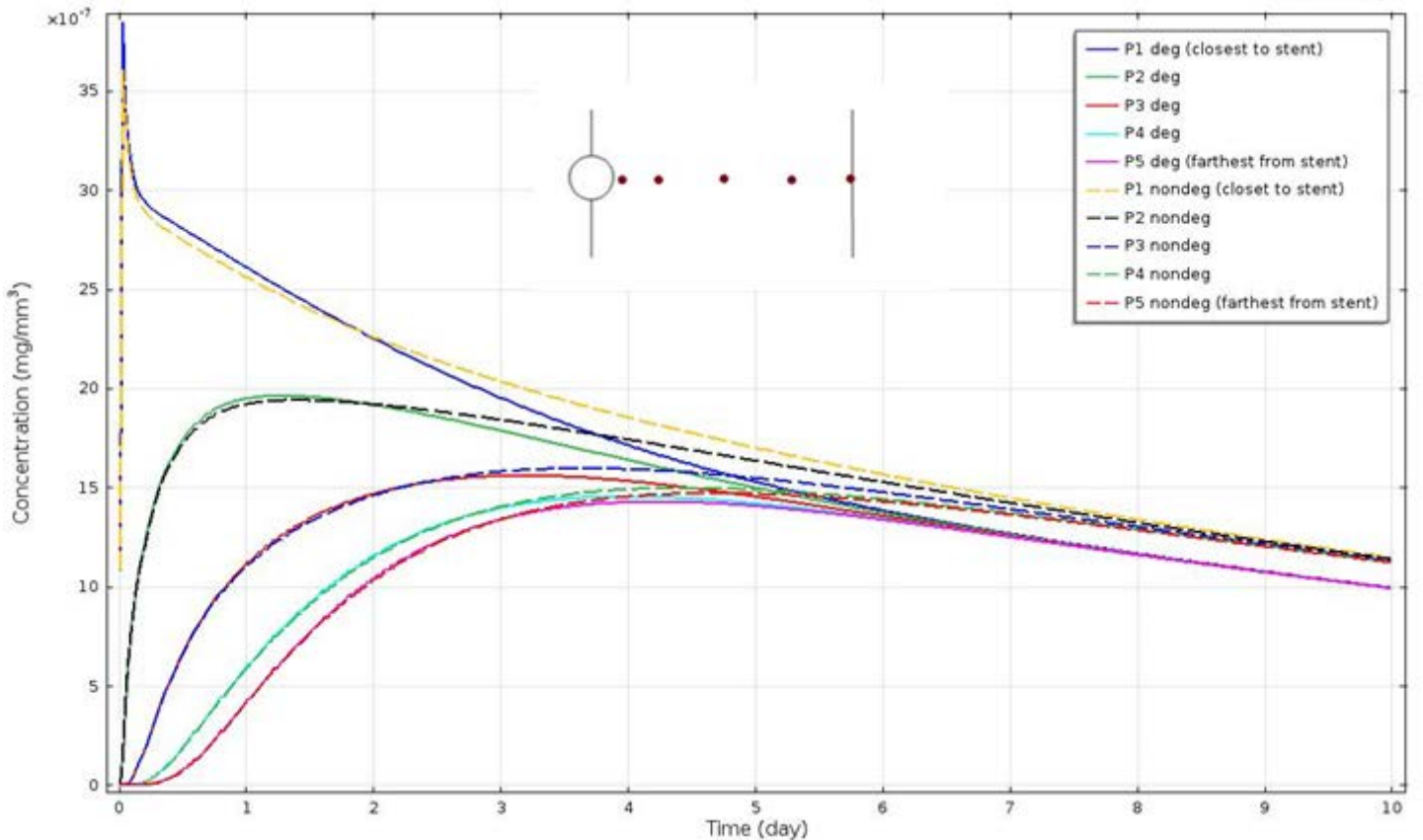


Figure 4: Concentration profiles at different depths in the colon wall for degrading and non-degrading models. The concentrations in the degrading model surpass the concentrations in the non-degrading model after approximately two days, and converge at a late time than the non-degrading model.

Figure 4 above shows a sharp peak in drug concentration at the new P1, due to the fact that this location is very close to the stent strut and drug diffusion occurs very rapidly at the onset of the simulation. For the other four points evaluated, there is a gradual rise in drug concentration due to diffusion from more concentrated areas, followed by a subsequent decrease in concentration due to degradation of the drug in the colon. A point that is closer to the stent strut reaches its maximum concentration earlier than a point that

is far away from the stent. When we compare the profiles of the degrading model (solid lines in Figure 4 above) with those of the non-degrading model (dashed lines), we can see that the profiles are very similar to each other at the beginning of the simulation. However, towards the latter half of the simulation, the concentrations at different depths in the degrading model converge much earlier and to a lower concentration (by approximately 10%) than the concentrations in the non-degrading model.

To visualize the difference in concentrations as a function of time, we plotted the percent difference in drug concentration between the degrading and non-degrading model at all five points.

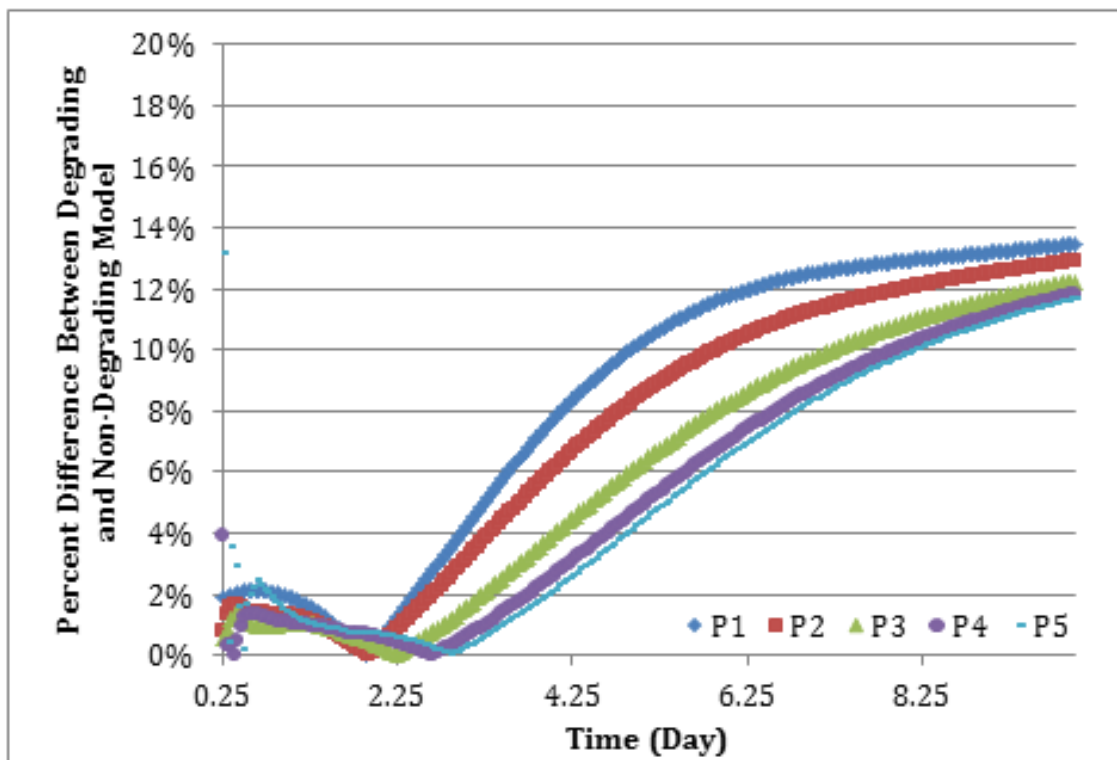


Figure 5: Percent difference in drug concentration between degrading and non-degrading model. The percent difference first decreases from day zero to day two, then increases from day two to reach a plateau of approximately 12% at day ten.

The horizontal axis starts at 0.25 day because of the extremely large (5000%) difference in drug concentration between the degrading and non-degrading model at the very early times. We speculated that this is due to computational uncertainty caused by time discretization, as concentrations change faster at the beginning. However, due to the long computation time for our model, especially for sensitivity analysis, reduction in time step was not implemented. From day two to day ten, the differences in drug concentrations increase with time. P1 has the fastest increase and P5, the slowest. The

differences in concentration start to plateau around day ten. At the end of the simulation, the concentration at P5 is approximately 12% lower for the degrading model than for the non-degrading model, while the concentration at P1 is approximately 14% lower. Therefore, the incorporation of stent degradation has a 12% to 14% impact on the drug concentration achieved in the colon wall. Stent degradation decreases the amount of drug available for diffusion. In the long run, a smaller amount of drug has diffused into the colon, which leads to lower converged concentrations than in the non-degrading model.

B. Objective 3: Assess the Feasibility of a Degradable Drug-Eluting Stent

Our third objective is to assess the feasibility of a drug-eluting stent that degrades with time in the application of minimally invasive therapy against CD. From Figure 4 above, we determined the maximum drug concentration in the colon, the average drug concentration at the end of ten days, the time of convergence, and the average drug concentration at convergence. The time of convergence is obtained by calculating the difference in concentration between P1 and P5 as a function of time. This difference is then expressed in percentage form $((P1-P5)/P5*100)$. As an uncertainty value of 5% is commonly used in comparing two values, we decided to use a cut-off value of 5% for the difference in concentration between P1 and P5. In other words, the concentrations are considered having converged if the percent difference is less than 5%. Table 1 details the values of the four parameters described above.

Table 1: Output parameter values for degrading model

Parameter	Value
Maximum Concentration	3.849e-6 mg/mm ³
Average End Concentration	9.923e-7 mg/mm ³
Time of Convergence	5.3 days
Average Concentration at Convergence	1.43e-6 mg/mm ³

The maximum concentration can be compared with the threshold for toxic concentration of infliximab in the colon wall. However, we were unable to obtain this data. Nonetheless, we ensured that our model's safety by using a safe dosage of initial drug concentration in the stent (Appendix A). We compared our average drug concentration at the end of ten days to the minimum therapeutic level required for 95% of the patients to display responsiveness to treatment, 5e-7 mg/mm³ (Steenholdt, 2011). Our end concentration is approximately twice the minimum level required. Therefore, our stent is effective in inciting response in CD patients for the duration of its use.

Next, we seek to compare the time of convergence to the time of complete stent degradation. After convergence of the concentrations, the colon wall has a uniform drug

concentration profile. This means that the affected CD region is being treated uniformly. Thus, the earlier the concentrations converge, the better it is for our application. To compare the time of convergence to the time needed for the stent to degrade, we plotted the drug concentration fractions in the colon wall on the same graph as the stent volume fraction.

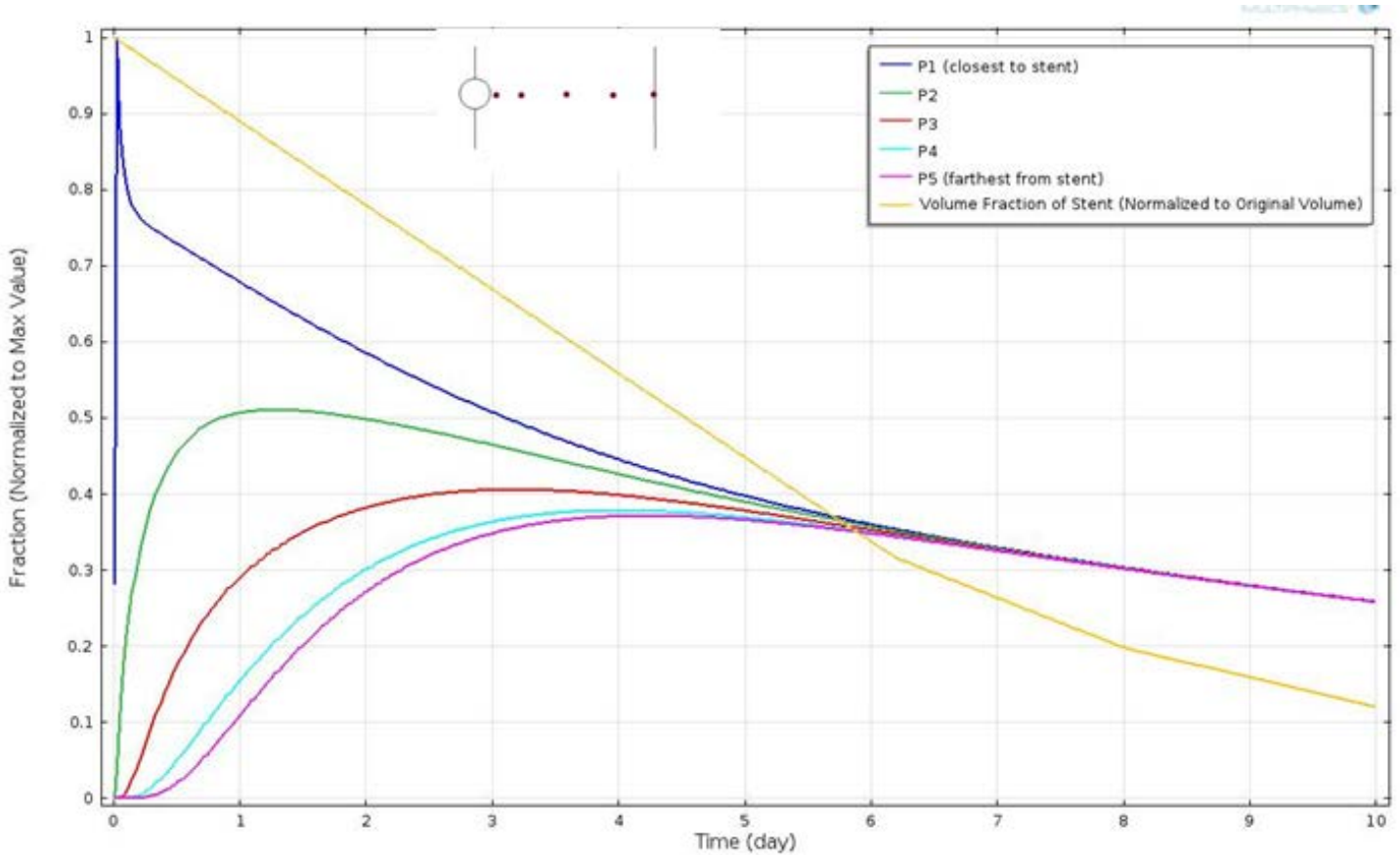


Figure 6: Drug concentration fractions at different depths and stent volume fraction with time. The stent degrades to 12% of its volume by day ten, while the concentrations converge by day 5.3.

In Figure 6 above, the drug concentrations were divided by the maximum concentration observed in the colon to obtain fraction values that range from 0 to 1. Similarly, the volume of the stent struts was divided by the initial volume of the stent struts to obtain fractions value from 0 to 1 that can be plotted with the concentration fraction values. The stent volume decreases linearly, and reaches about 12% of its initial volume at the end of our simulation. We can see three distinct slopes for the stent degradation line; these are due to the fact that stent degradation velocity depends on time. Detailed explanation of the how the velocities were obtained can be found in Appendix A. Figure 6 shows that the time of convergence, at 5.3 days, occurs before the time the stent degrades to 10% of its original volume. Therefore, uniformity in drug concentration

is achieved before the stent disappears from the colon. This is desirable because it shows that drug diffusion occurs faster than stent degradation. If the inverse was true, then most of the drug would have been wasted rather than diffused into the tissue. Diffusion would have been cut short when the stent disappears from the colon, leading to low efficiency.

C. Objective 4: Determine the Effect of Composition on Stent Degradation

Stent degradation can be controlled separately from diffusion. Researchers can modify the percentage of the monomers making up the stent material to alter its degradation velocity. While determining the effect of stent composition on the rate of stent mass loss is whole new research question, we sought to correlate different rates of mass loss, obtained from literature, to stent degradation velocity ($\frac{dr}{dt}$) and stent volume change. To this end, we implemented stent degradation by itself, without drug diffusion. We obtained the different rates of mass loss in literature (see Appendix A), and translated them to different degradation velocities (for detailed calculations see Appendix A). We then plotted the volume fraction of the stent with respect to time for different degradation velocities. The length of the study was set to twenty days. The time the stent reaches 10% of its initial volume varies accordingly. Thus, we can optimize the drug-eluting stent by choosing a composition that yields a degradation velocity that is appropriate for the duration of use.

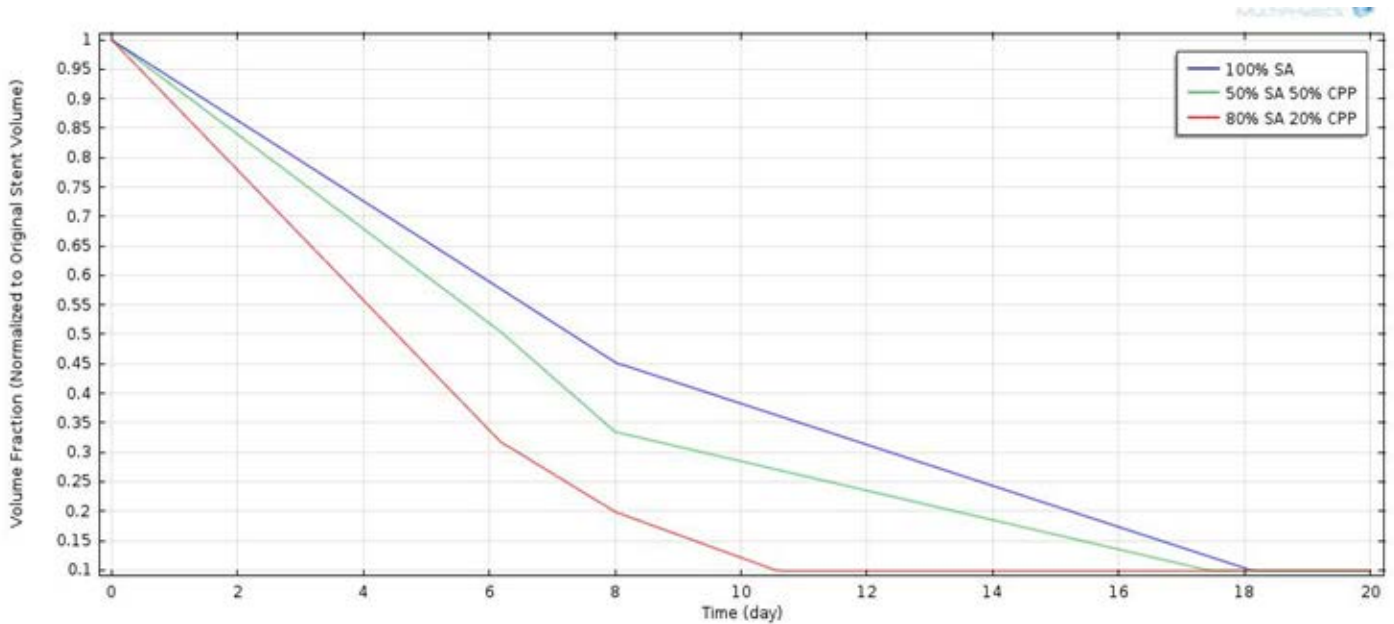


Figure 7: Stent volume fraction for different stent compositions as a function of time. 20:80 CPP-SA has the fastest degradation, while 100% SA has the slowest degradation.

According to Figure 7, varying the ratio of CPP to SA in the copolymer significantly alters the time the stent takes to degrade to 10% of its original volume. While 20:80 CPP-SA takes approximately 10.5 days to achieve 90% degradation, 50:50 CPP-SA takes 17.5 days, while 100% SA takes 18 days. The rate of volume decrease is different for each stent composition, evidenced by the differing slopes in Figure 7. While Figure 7 only contains three types of stent compositions, it is possible to construct more curves so that an engineer can decide on the stent composition based on the desired stent degradation profile.

D. Objective 5: Determine the Effect of Input Parameter Variation on Output Parameter Values Through Sensitivity Analysis

We performed sensitivity analysis on our model to determine how changes in parameter values impact the diffusion behavior of the stent, and therefore the end results of our study. Sensitivity analysis also tells us which parameter needs to have the most accurate value in our model. We performed sensitivity analysis on the degrading model, which coupled mass transport and deformed geometry. The specific parameters that we varied are: drug degradation rate in the colon, infliximab diffusivity in the stent, infliximab diffusivity in the colon, and stent strut radius. As outlined in the degrading model analysis subsection, we are interested in the following output parameters: maximum concentration in the colon, the average concentration at the end of the ten-day study, the time of concentration convergence, and the average concentration at convergence. Therefore, we seek to determine how varying each parameter affects each of the output parameters described above.

Due to limited amount of research on stent delivery of infliximab, we were unable to clearly establish a range of parameter that corresponds well to literature values. Therefore, for the rate of drug degradation in the colon and the two diffusivity values, we elected to use a range that spans one order of magnitude and includes the parameter value we used in our model. Table 2 below contains the exact values for each parameter in our sensitivity analysis.

Table 2: Input parameter values used for sensitivity analysis

Rate of drug degradation (mg/mm ³ s)	Diff. in Stent (mm ² /s)	Diff. in Colon (mm ² /s)	Stent Strut Radius(mm)
5E-07	1E-08	1E-06	0.12
7E-07	4E-08	4E-06	0.135

9E-07	7E-08	7E-06	0.15
1E-06	1E-07	1E-05	

The input parameters were varied by one order of magnitude.

The following results were obtained.

i. Maximum Concentration

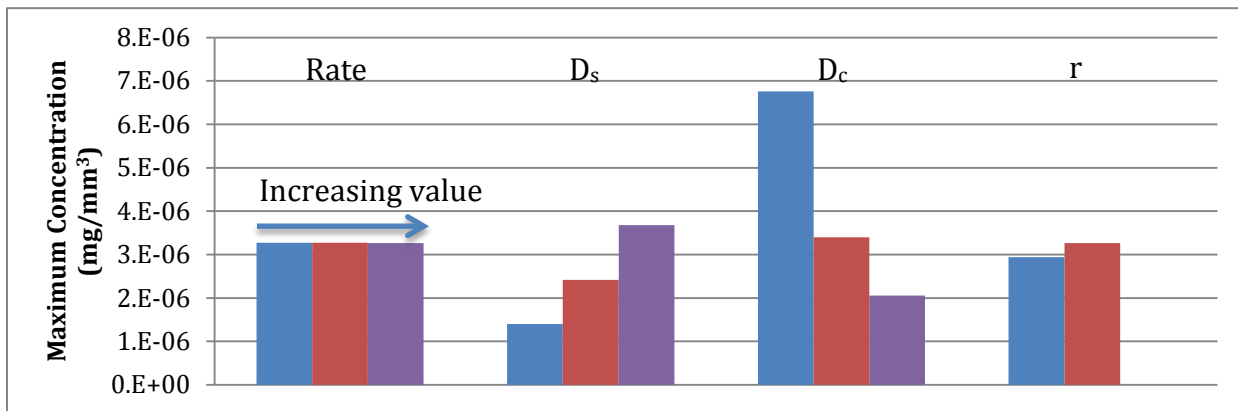


Figure 8: Effect of variation in input parameters on the maximum drug concentration in the colon. Drug diffusivity in colon has the greatest effect on the maximum concentration, followed by diffusivity in stent.

According to Figure 8, varying the rate of drug degradation in the colon has almost no effect on maximum concentration, which is to be expected, since maximum concentration mainly concerns initial diffusion of drug from stent into the colon wall. As a result, the maximum concentration is sensitive to both diffusivity values. Increasing the drug diffusivity in the stent means that drugs diffuse out of the stent faster, therefore leading to an increase in maximum concentration. Increasing the diffusivity in the colon means drug diffusing away from stent faster, therefore leading to lower maximum concentration. The maximum concentration is more sensitive to diffusivity in the colon.

ii. Average Concentration at End of Study

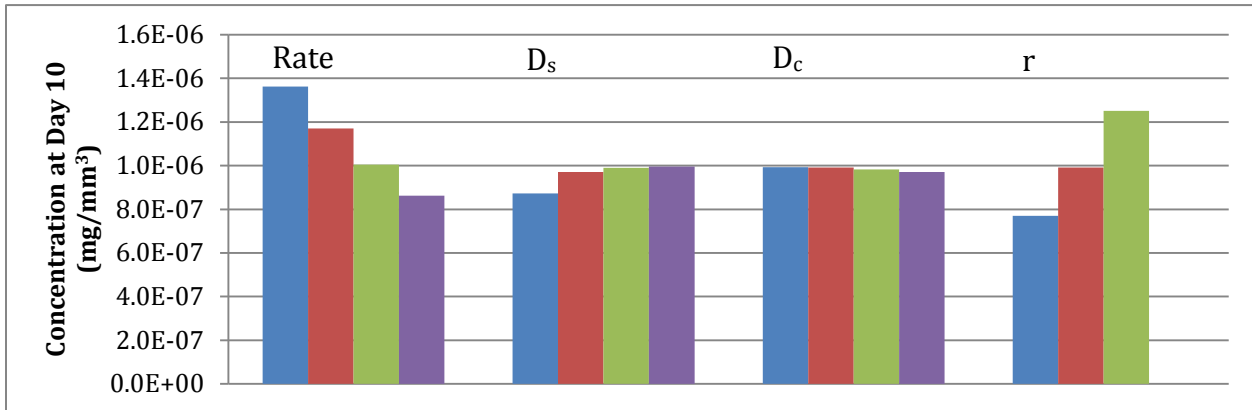


Figure 9: Effect of variation in input parameters on the average drug concentration in the colon at end of study. Drug degradation rate and stent dimensions have greater effect on the average end concentration.

Increasing the rate of drug degradation leads to faster drug removal in the colon, therefore leading to lower drug concentration in the colon wall. Increasing the radius of the stent means greater amount of drug available, therefore increasing the end drug concentration. The average end concentration is most sensitive to stent dimensions.

iii. Time of Convergence

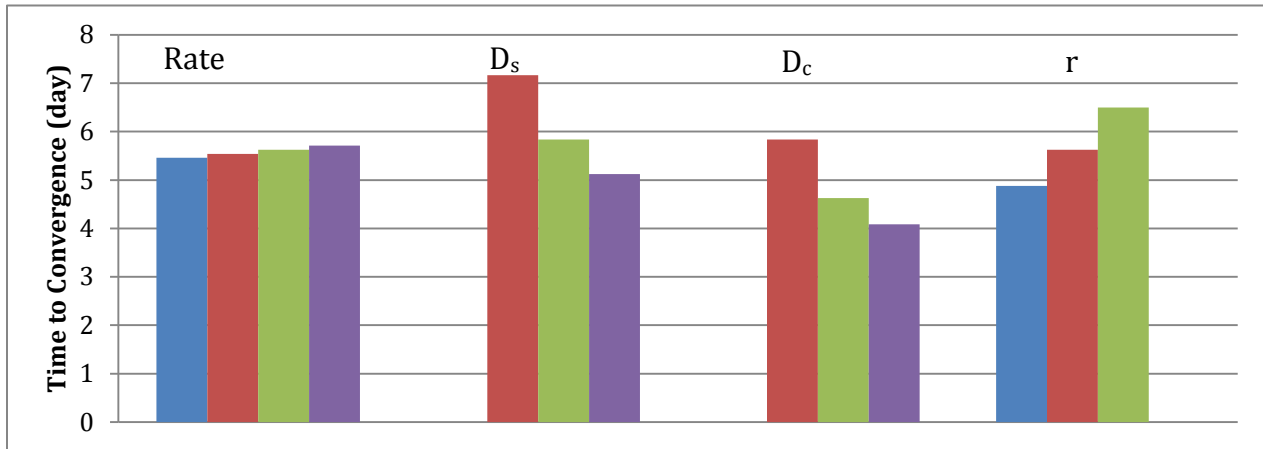


Figure 10: Effect of variation in input parameters on time of convergence. The two diffusivity values have greater effect on time of convergence.

The time of convergence is sensitive to all input parameters but the rate of drug degradation. This is because concentration convergence depends on diffusive behaviors of the drug in the colon, while drug degradation is uniform in the colon. For both

diffusivities, a larger value leads to faster diffusion, and hence an earlier achievement of concentration convergence.

iv. Average Concentration at Convergence

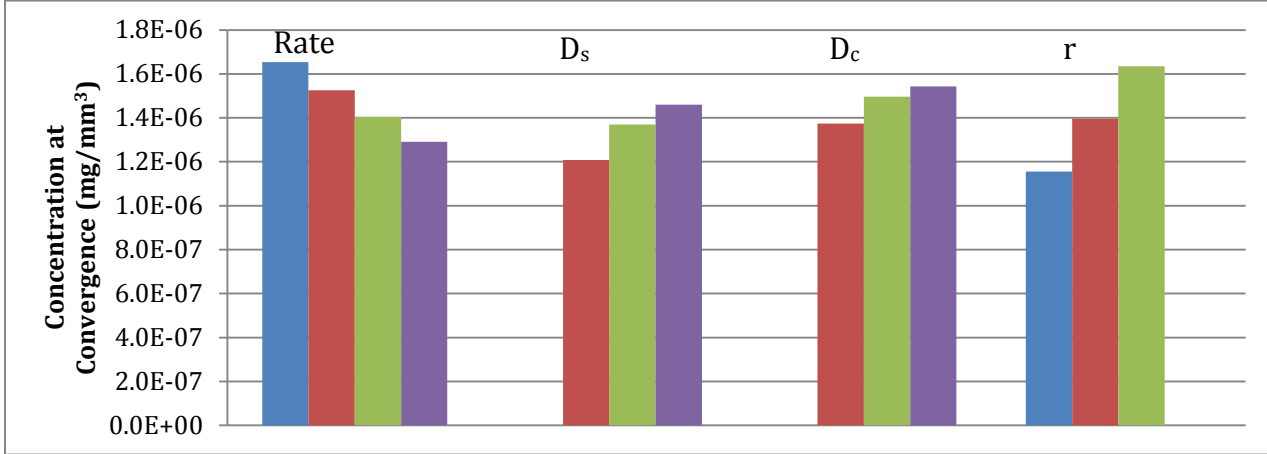


Figure 11: Effect of variation in input parameters on average concentration at convergence. Stent dimensions have greater impact on average drug concentration at convergence.

Increasing the rate of drug degradation decreases the average concentration at convergence similarly to the way it decreases end concentration. Increasing diffusivity in stent and in colon both lead to increasing concentration at convergence. Increasing stent dimensions also leads to increasing concentration at convergence. Concentration at convergence is more sensitive to stent dimensions.

E. Accuracy Check

Given the novelty of our proposal, there is limited literature on modeling drug diffusion from a stent in the colon. Most studies concern with drug diffusion in cardiovascular stents. However, the presence of blood flow, and as a result, convective mass transport in addition to diffusion, prevents us from comparing our model to existing experimental studies. There, we are limited to comparing our numerical model with an analytical model of a drug release from polyhedral oligosilsesquioxane thermoplastic polyurethanes (POSS TPUs) (Guo, 2002). This particular analytical model takes into account Fick's diffusion and polymer degradation. Therefore, we are comparing our coupled diffusion and degradation model with the analytical solution provided. Three critical prerequisites make the POSS TPU model comparable and applicable as our validation model:

- 1) In the POSS TPU model, stents infused with drug are statically immersed in PBS buffer to test drug release rate. There is no flow of PBS in experimental set-up, and this is consistent with one of the assumptions in our model that no convective drug transport is considered in colon wall or lumen.
- 2) The POSS TPU model includes polymer degradation.
- 3) The POSS TPU coat is a surface-eroding material which matches the property of our surface-eroding drug-eluting stent.

The analytical solution given by Guo et al. is for the cumulative fractional drug release $f(t)$ (total amount of drug released with time divided by total amount of drug infused) with respect to time, and is given by Eq. 9.

$$f(t) = 1 - \exp \left[-2 \left(\frac{D_0 \exp(kt) \cdot t}{\pi \delta_0^2 (1 + \lambda t)^2} \right)^{0.5} \right] \quad \text{Eq. 9 (Guo, 2002).}$$

Where $D_0 \exp(kt) = D_s$ in our model, as our diffusivity in stent stays constant with time; δ_0 is the polymer thickness at time $0 = r_i$ in our model; λ is the rate of polymer thickness change = cst/r in our model, where r is the time-dependent radius of the stent.

Thus, substituting in our parameter values (Appendix A), we obtained a plot of the cumulative fractional drug release with respect to time with Matlab.

To compare the analytical solution to our model, we found the cumulative fractional drug release by subtracting the total amount of drug still left in the stent at any given time t from the total initial drug loaded. The total amount of drug still left in the stent was found by multiplying the concentration of drug at any time t in the stents by the volume of the stent struts. In other words:

$$f(t) = \frac{V_i C_i - V(t) * C(t)}{V_i C_i} \quad \text{Eq. 10}$$

When we plotted the cumulative fractional drug released computed from our model with the analytical solution, we obtain the following graph.

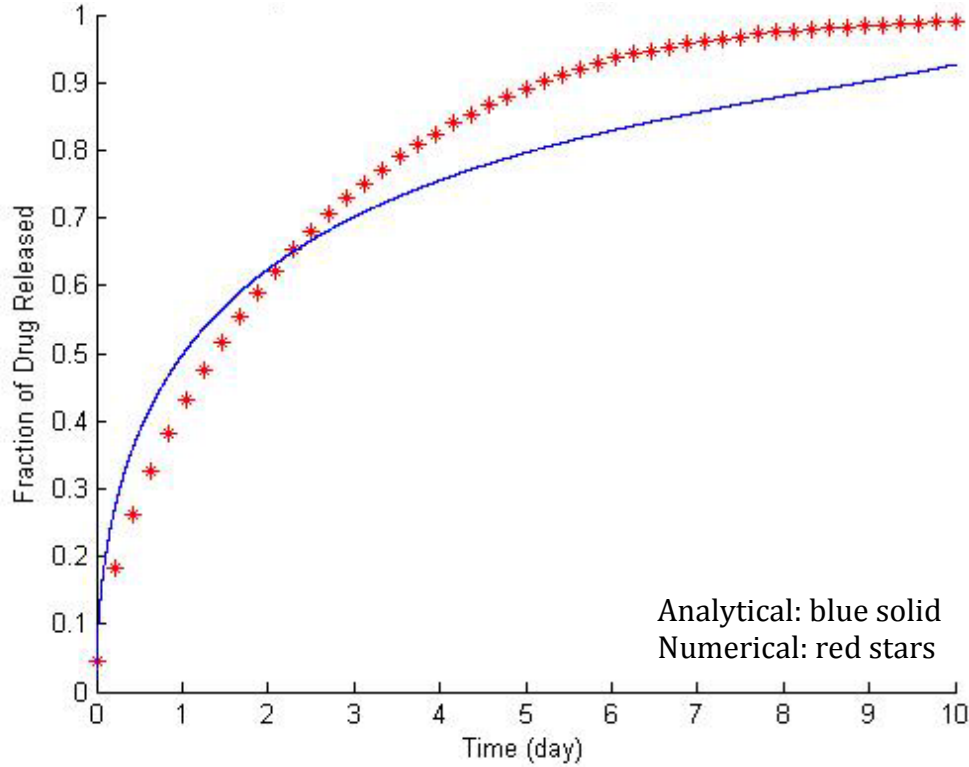


Figure 11: Cumulative fractional drug release versus time for analytical and numerical solutions. The numerical solution assumes a similar shape as the analytical solution. However, the numerical solution reaches 100% drug release by day ten, while the analytical solution reaches 92% by day ten.

In the graph, the blue curve is analytical solution plotted by MATLAB, and the red one is our numerical solution computed by COMSOL. The analytical solution and numerical solution have a similar trend. However, our model releases nearly 100% of the drug by day ten, whereas the analytical model releases a little over 92% of the drug by day ten. In addition, our model releases drug at a slower rate than the analytical solution at earlier times, and at a faster rate at later times. Through comparison and analysis, we mainly attributed the discrepancy between the two to the fact that in the analytical solution, stent degradation rate is one constant divided by radius of the stent, whereas in our numerical solution stent degradation rate constant assumes different values at different times. We calculated and input the average stent degradation rate in the validation model. Besides that, the validation model does not include drug degradation in the colon; however, in our model infliximab degrades in colon wall.

6. Conclusion and Design Recommendations

A. Conclusions

In conclusion, we have successfully developed a model in COMSOL to simulate the diffusion of infliximab from a drug-eluting stent placed in the colon, and track the concentration levels of infliximab in the colon wall with time. Our model has allowed us to compare drug diffusion behavior of both degrading and non-degrading stents. We have determined that incorporation of stent degradation decreases the drug concentration in the colon at the end of the study by twelve to fourteen percent. When we analyzed the coupled model of drug diffusion and stent degradation, we obtained an average drug concentration in the colon wall at the end of ten day of $9.923\text{e-}7 \text{ mg/mm}^3$, which is higher than the minimum cut-off concentration for 95% response to infliximab treatment in CD and colitis patients (Steenholdt, 2011). We obtained a time of convergence of 5.3 days, and a time for 90% stent degradation of 10.5 days. Therefore, our proposed design is a feasible and effective method to deliver infliximab locally and sustainably delivery infliximab to the colon wall. Furthermore, we determined the effect of changing stent composition on degradation velocity. Finally, we established the sensitivity of our model to input parameters. While we applied our model to a specific problem –diffusion of infliximab to treat CD, our proposal established a method that is applicable to many clinical needs in the GI tract, for instance other drugs to treat CD or other conditions. What we are providing is a framework to study drug diffusion from a stent-device in the GI tract. Compared to cardiovascular stenting, there is still much to be done in the field of GI stenting, and many clinical needs to be addressed.

B. Constraints and Limitations

We made several simplifying assumptions that may limit the applicability of our model. The colon is complex, with peristalsis and spasms that transport waste products, and hosts a rich and diverse bacterial population. Diffusion behavior exhibited in our model may not resemble the actual diffusion behavior in the colon.

To manufacture our product, additional research has to be performed on the compatibility of CPP-SA, or any other biodegradable material, with infliximab to determine if the stent can be successfully infused with the drug. Once the compatibility of the polymer-drug combination has been established, the stent can be infused with infliximab by mixing infliximab solution with liquid polymer solution. The resulting mixture is then molded into a stent shape. Colon stent manufacturing is relatively simple; the challenge lies in incorporating anti-migration features with the stent to prevent premature excretion of stent or perforation of the colon due to improper positioning.

Economically, the costs lie in preclinical and clinical studies necessary to ensure efficacy and safety of such device in a patient population. In terms of device manufacturing, the costs associated with infliximab-infused degradable stent should not exceed the costs of making current drug-eluting cardiovascular stents by much.

C. Design Recommendations

We suggest choosing a biodegradable polymer of the polyanhydride family and with a volume degradation rate of nine to ten percent per day. To achieve a uniform infliximab concentration in the colon wall that is above the minimum therapeutic level, an initial concentration of $5\text{e-}5 \text{ mg/mm}^3$ of infliximab can be infused into the stent. We propose a stent radius of 0.135 mm, and spacing between two struts of 0.50 mm.

Appendix A: Mathematical Statement of the Problem

A. Governing Equation

The governing equation for mass transfer in our study is:

$$\frac{\partial C}{\partial t} = D \left(\frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right) + \frac{\partial^2 C}{\partial z^2} \right) + R \quad \text{Eq. 1}$$

Whereas C is the concentration of infliximab; D is diffusivity of infliximab, and has different values in the stent and in the colon wall; R represents the rate of consumption/degradation of infliximab in the colon wall tissue.

The degradation of infliximab in the colon wall is assumed to follow first-order kinetics (Fasanmade, 2009). The equation for drug degradation in the colon wall thus follows:

$$C = C_i e^{-kt} \quad \text{Eq. 2}$$

Where the degradation constant k is calculated from the half-life of the drug with the following equation:

$$k = \frac{\ln(2)}{t_{\frac{1}{2}}} \quad \text{Eq. 3}$$

The half-life of infliximab in the colon tissue is 210 hours (756000 seconds) (FDA). The degradation constant k is calculated to be $9.1686e-7 \text{ s}^{-1}$. The rate of degradation R in the governing equation is $R = \frac{dC}{dt} = -k * C = -9.1686e-7 * C$.

B. Boundary and Initial Conditions

i. Boundary conditions

All external boundaries are assumed to have a zero flux.

$$-D \frac{dc}{dr} = 0 \text{ and } -D \frac{dc}{dz} = 0$$

Given that the colon thickness, 1.6 mm, is much greater than the radius of the stent, 0.135 mm, the colon wall effectively behaves as a semi-infinite region, with zero concentration gradient and hence zero flux at its far end. The midline of the stent is a symmetry axis, therefore also having a flux of 0. Finally, we assume that there is no convective transport of drug to the lumen. Unlike the arteries, the colon does not have a regular flow, but instead has peristalsis and irregular spasms to move contents around.

This irregular flow is too complex for the scope of our project. Therefore, we assumed a zero flux at the stent-lumen boundaries.

ii. Initial conditions

In stent: $C_i = 5e - 5 \frac{mg}{mm^3}$ (Merck, 2013)

In colon wall: $C_i = 0 \frac{mg}{mm^3}$

C. Stent Material Degradation

Degradable polymers used in medicine degrade either by bulk erosion or surface erosion. Bulk eroding biomaterials include poly-hydroxy acids such as PLA, PGA, PLGA, and PLLA. Surface eroding biomaterials include polyanhydrides such as CPP: SA copolymer. Although PLA and PGA are widely used as stent materials, they degrade rather slowly, over weeks (Göpferich & Tessmar, 2002). Given our study length of ten days, we wanted to use a material that almost completely degrades by the end of our study, to minimize any side effects caused by the prolonged presence of stent materials in the colon, which have been known to cause in some cases perforation, migration and infection (Roldan, 2012). Polyanhydrides, on the other hand, possess very reactive functional groups that degrade by hydrolysis. Therefore, we decided to use one polyanhydride that is commonly used in drug delivery - poly[1,3-bis(*p*-carboxyphenoxy)propane-*co*-sebacic acid] (*p*(CPP-SA)).

The degradation kinetics of *p*(CPP:SA) were quantified in an *in vitro* experiment conducted by Göpferich and Tessmar in 2002. Cylindrical matrices of *p*(CPP:SA) were eroded in phosphate buffer at a pH of 7.4 and 37 degrees Celsius. Percent monomer release was measured with time for three different compositions of copolymer matrices: 100% SA, 20:80 CPP-SA and 50:50 CPP-SA. The degradation velocity of the 20:80 CPP-SA material (70% mass loss in 6 days) corresponds best to what we need in our model (Göpferich and Tessmar, 2002).

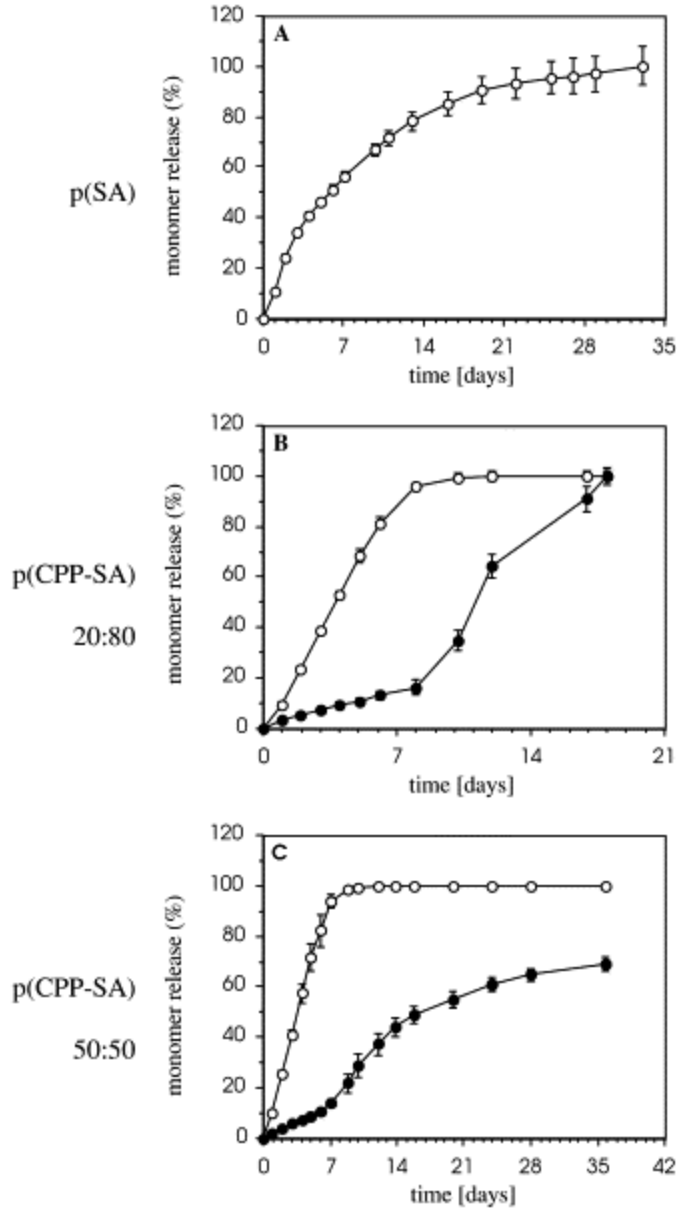


Figure 12: Rate of monomer release versus time for different compositions of CPP-SA. Matrices were eroded in phosphate buffer at 37 degrees. (Göpferich & Tessmar, 2002).

The percent monomer release can be used to calculate the change in mass over time. To do so, we looked at the slope of the percent monomer release versus time from zero to ten days. We divided the time into three periods with different slopes: 0 to 6.2 days, 6.2 to 8 days and 8 to 10 days. For each time period, we took the slope of each monomer, and calculated the weighted slope for the copolymer. For example, for the 20:80 CPP-SA and from 0 to 6.2 days, 13.33% mass of SA lost per day and 2% mass of CPP lost per day led to 11.0664% mass of copolymer per day. Table 3 below contains the rates of mass loss (in percent/second) for all three compositions and for all three time periods.

Table 3: Rates of mass loss (%/s) for 20:80 CPP-SA (cM)

Day	0 – 6.2	6.2 – 8	8 - 10
SA	9.33e-5%	3.22e-5%	5.79e-5%
20:80 CPP-SA	1.28e-4%	7.56e-5%	4.51e-5%
50:50 CPP-SA	7.47e-5%	4.82e-5%	2.89e-5%

Rates of mass loss in percent per second are then converted to decimal and referred to as cM.

**Figure 13:** One stent strut modeled as a torus. The stent strut has R of 30 mm and initial r of 0.135 mm.

In our study, the stent is modeled a series of tori with spacing in between each two. Hence, as shown in Figure 13, each stent strut is a torus with R being the distance between the center of the stent strut to the middle of the lumen, and r the radius of the stent strut. Stent degradation occurs when r decreases with time. We next correlated the rate of mass change ($\frac{dM}{dt}$) of each stent strut to the rate of r change ($\frac{dr}{dt}$) in the following way. The percent mass change of the polymer material is the same as the percent volume change, as the density of the material remains the same in surface erosion. Therefore, within each time period, the rate of volume change is equal to $cM \cdot V_i$, where cM, also a constant, is the percent mass release, in decimal form, in each entry of Table 3, and V_i is the initial volume of each stent strut.

$$V_i = 2\pi R\pi r_i^2 \quad \text{Eq. 4, where } R = 30 \text{ mm and } r_i = 0.135 \text{ mm}$$

Therefore, $\frac{dV}{dt} = cM * 2\pi R\pi r_i^2$ Eq. 5.

Next, we rewrote $\frac{dV}{dt}$ in terms of $\frac{dr}{dt}$:

$$\frac{dV}{dt} = 4\pi^2 Rr \frac{dr}{dt} \quad \text{Eq. 6}$$

$$\frac{dr}{dt} = \frac{dV}{dt} \left(\frac{1}{4\pi^2 Rr} \right) = \frac{cM * 2\pi R\pi r_i^2}{4\pi^2 Rr} = \frac{cM r_i^2}{2} \frac{1}{r} \quad \text{Eq. 7}$$

Eq. 7 can be rewritten as $\frac{dr}{dt} = \frac{cst}{r}$ where $cst = \frac{cM r_i^2}{2}$.

Therefore, $\frac{dr}{dt}$ is inversely proportional to r. We then plugged in different cM values for different time periods, and set the resulting function to be our mesh velocity.

As the stent struts become smaller and smaller with time, the contours of the struts began to display wrinkling, due to difficulty in meshing increasingly small regions. Therefore, we elected to terminate stent degradation when the resulting stent strut has reached 10% of its original volume.

D. Input Parameters

The following table summarizes all the input parameters in our model, and their sources in literature.

Table 4: Input parameters used in the model

Input Parameter	Value/Expression	Unit	Source
Thickness of colon wall	1.6	mm	(Wiesner, 2002)
Radius of colon (from lumen center to colon wall)	30	mm	(Jones, 1969)
Radius of stent	0.135	mm	(Pavlidis, 2011)
Spacing between two struts	0.50	mm	(Pavlidis, 2011)
Length of stent	15	mm	(Boston Scientific)
Diffusivity of infliximab in colon (D_c)	4.292e-6	mm ² /s	(Hicks, 2006)
Diffusivity of infliximab in stent (D_s)	7.725e-8	mm ² /s	(Zhang, 2003)
Infliximab half-life ($t_{1/2}$)	756000	s	(FDA)
Degradation rate constant of infliximab in colon (k)	9.1686e-7	1/s	(FDA)
Stent degradation rate constant (cst) Day 0 – Day 6.2	1.17e-08	mm ² /s	(Gopferich & Tessmar, 2002)
Stent degradation rate constant (cst) Day 6.2 – Day 8	6.91e-09	mm ² /s	(Gopferich & Tessmar, 2002)
Stent degradation rate constant (cst) Day 8 – Day 10	4.11e-09	mm ² /s	(Gopferich & Tessmar, 2002)
Initial concentration	5.00e-5	mg/mm ³	(Merck)
Terminal volume fraction of stent	10%		N/A
Convergence Concentration Threshold	5%		N/A

This table contains all of the dimensions, physical and chemical properties, and rate constants utilized in this model. The length of a complete stent averages 60 mm. A length of ¼ of the entire stent (15 mm) was taken as the stent length in our model.

Derivation of Input Parameters

i. Diffusivity of infliximab in the colon

Studies conducted on the effectiveness of infliximab as a therapy for Crohn's Disease mainly focused on clinical effectiveness of oral infliximab administration, judged by endoscopic images of CD lesions and the presence of complications such as stricture and fistulas. Due to the novelty of our design project, there is scarce literature data on diffusion behavior of infliximab through the colon wall. Therefore, exact value of infliximab diffusivity in the colon wall was not obtained. Instead, we used the diffusivity of tirapazamine (TPZ), an anti-cancer drug, in HT29 colon cancer multicellular layers (Hicks, 2006), corrected with the molecular weight of infliximab. The equation we used to correlate diffusivity and molecular weight is for proteins and large molecules in water: $D_{A,water} \propto \frac{1}{M_w^{\frac{1}{3}}}$ Eq. 8 (Saltzman, 2001). Although in reality we are looking at diffusion in

the colon wall tissue, we assumed the general relationship between diffusivity and molecular weight is the same in water and in tissue. After all, tissues are mainly composed of water. Therefore, the corrected diffusivity of infliximab is:

$$D_{i,c} = D_{TPZ,colon} * \frac{Mw_{TPZ}^{\frac{1}{3}}}{Mw_i^{\frac{1}{3}}} = 4e - 5 \frac{mm^2}{s} * \frac{(178.148 Da)^{\frac{1}{3}}}{(114190.3 Da)^{\frac{1}{3}}} = 4.292e - 6 mm^2/s$$

ii. Diffusivity of infliximab in the stent

Infliximab has not yet been incorporated into a stent as an eluting drug. Therefore, exact value of its diffusivity in CPP: SA polymer was not found. Instead, we used the diffusivity of BSA from the surface-eroding material TMA-Tyr/Sa/PP 40:30:30 found in a research article (Zhang, 2003). The effective diffusivity of the solute in the polymer is given by the equation:

$$D = D_o * \frac{\varepsilon}{\tau} \text{ Eq. 9, where } D_o \text{ is } 8.3e-11 \text{ m}^2/\text{s}, \varepsilon = 0.3, \text{ and } \tau = 249 \text{ (Zhang, 2003).}$$

The effective diffusivity of BSA in TMA-Tyr/SA/PP 40:30:30 is therefore $1e-7 \text{ mm}^2/\text{s}$. We then converted this diffusivity value to the value we implemented in our model by correcting for the molecular weight using Eq. 8. The diffusivity of infliximab we obtained is:

$$D_{i,c} = D_{BSA,polymer} * \frac{Mw_{BSA}^{\frac{1}{3}}}{Mw_i^{\frac{1}{3}}} = 1e - 7 \frac{mm^2}{s} * \frac{(66,463 Da)^{\frac{1}{3}}}{(114,190.3 Da)^{\frac{1}{3}}} = 7.725e - 8 mm^2/s$$

We realize that the above diffusivity is still for the TMA-Tyr/SA/PPG 40:30:30, and not for our 20:80 PPG: SA. However, due to scarcity of literature data, we assumed the two surface-eroding materials are similar to each other in terms drug diffusion behavior.

iii. Initial infliximab concentration in the stent

The initial infliximab concentration in the stent is derived from the blood injection dosage for infliximab given by Merck. It is recommended that a dosage of 5mg/kg of body mass should be administered once in a two-week period. Our stent is designed to replace the blood injection to minimize systematic exposure to the aggressive biologic agent infliximab. Therefore, we decided to use the same dosage for our stent. We converted the dosage to a concentration value by first assuming a body mass of 60kg for an average female Crohn's patient and a total blood volume of 6 L. Assuming the entire infliximab dose after injected is pumped by the heart to blood vessels throughout the body, and is uniformly distributed in the body, then the initial blood concentration level of infliximab is $C_{i,blood} = \frac{5\frac{mg}{kg} * 60kg}{6L} = 50 \frac{mg}{L} = 5e - 5 \frac{mg}{mm^3}$. We set this concentration to be the initial drug concentration in the stent.

$$C_{i,stent} = C_{i,blood} = 5e - 5 \frac{mg}{mm^3}$$

iv. Minimum infliximab therapeutic level in the colon

According to literature research, a cut-off value of 0.5 µg/mL for infliximab trough level concentration was correlated with 95% of patients being sensitive to CD treatment using infliximab (Steenholdt, 2011). Therefore, we used this threshold as the minimum therapeutic value in our model. We converted 0.5 µg/mL to the units of mg/mm³ and obtained 5e-7 mg/mm³.

Appendix B: Solution Strategy

A. Solver Configurations

We conducted three studies in our project: drug diffusion coupled with stent degradation, drug diffusion alone, and stent degradation alone. In the drug diffusion coupled with stent degradation study, both transport of dilute species and deformed geometry modules were implemented. The model was run for ten days, or 864000 seconds, because stents placed in the colon have a tendency to be expelled after an average of seven to ten days (de Roberto, 2012). To balance the precision of the solutions with the time the software takes to compute the model, a time stepping of 30 minutes was implemented. The direct solver PARDISO was used to compute the model. The relative tolerance is 0.01, while the

absolute tolerance is 0.001. Tolerances ensure that when the concentration of infliximab in each free quadrilateral element has an error below 0.001. In the drug diffusion alone study, only transport of dilute species was implemented. The solver parameters and setting were the same as the first study. In the stent degradation alone study, only deformed geometry was implemented. The model was run for twenty days, to provide a wider time period, and the time stepping was set to 60 minutes, to decrease the computation time. All other solver parameters remained the same.

B. Mesh Development and Convergence

We have chosen to use free quadrilateral elements to mesh our geometry, because our model involves deformed geometry. In other words, as the stent struts shrink with time, the mesh in our model would also change with time. We have decided to have a denser mesh near the stent boundaries (the luminal side), as these are the regions where we expect to see a greater and faster change in concentrations. We performed mesh convergence in our model with determine the optimum number of elements to be used.

In our mesh convergence analysis, we varied the maximum element size, the minimum element size, and the maximum element growth rate to obtain different number of elements. We obtained 3347, 3492, 6107, 15253 and 26654 elements for our mesh convergence analysis. We plotted the concentration at a point that is located near the stent strut, 30.3 mm from the lumen center and 6.55mm from the stent midline, at 604800 seconds after stent placement. The closer the point is to the stent struts, the more sensitive the concentration of infliximab is at that location. Figure 14 below shows the concentration of infliximab versus the number of elements meshed.

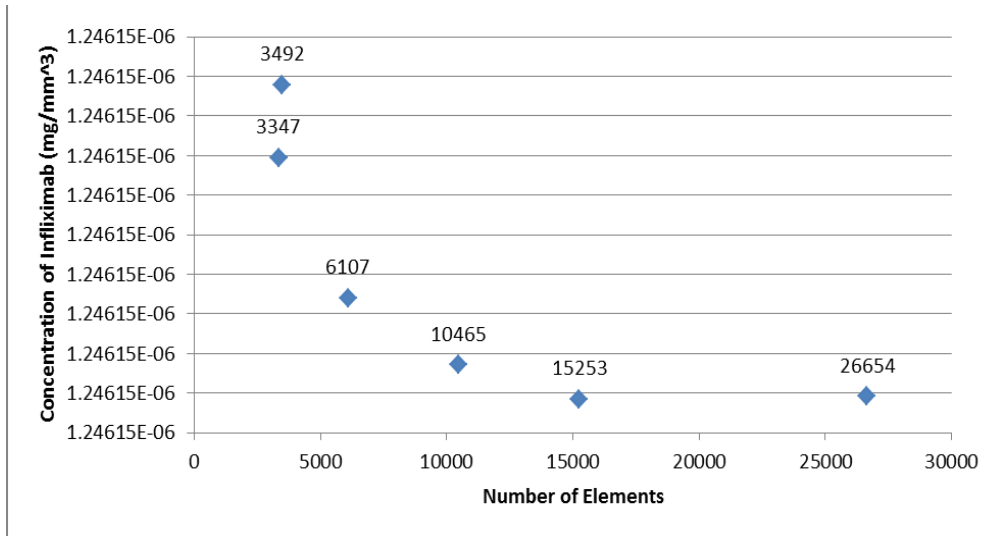


Figure 14: Concentration of infliximab versus the number of elements at 604800 seconds after stent placement. Mesh convergence achieved with 15253 elements.

According to Figure 14 above, the concentration of infliximab at (30.3 mm, 6.55 mm) at 604800 seconds begins to converge at 15253 elements. When the number of elements is further increased to reach 26654, the concentration shows minimal changes. We performed a second mesh convergence to determine the concentration at an earlier time, 126000 seconds, to determine if time affects the optimal number of elements. Mesh convergence was again reached with 15253 elements. Therefore, we meshed our geometry using 15253 free quadrilateral elements. More specifically, the maximum element size is 0.05 mm, the minimum element size is 1e-4 mm, and the maximum element growth rate is 1.05. Figure 15 below shows a cut-off of the mesh for the top three stent struts for better visualization. In actuality, complete geometry in Figure 1d was meshed.

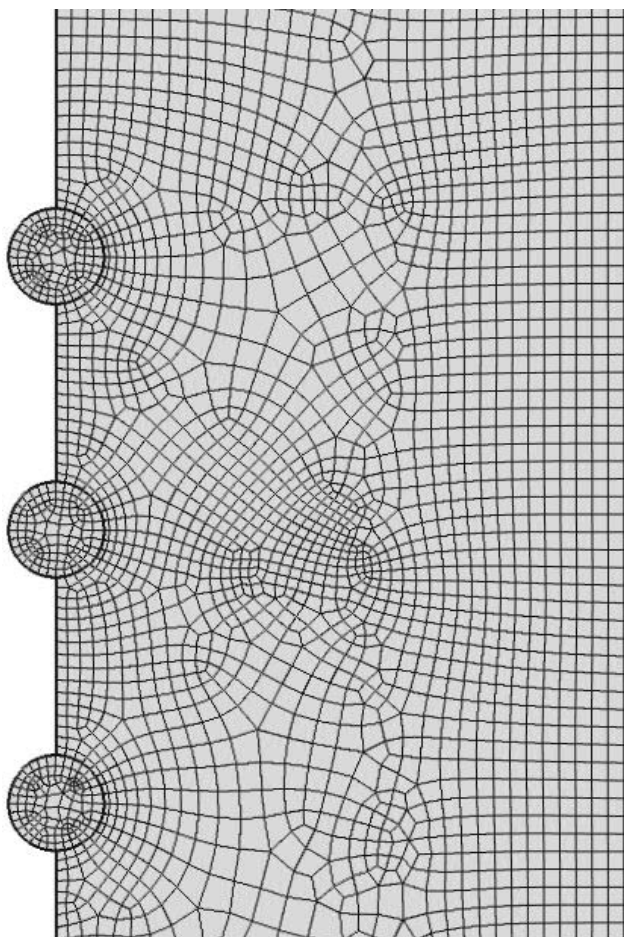


Figure 15: Cut-out mesh showing only the top three stent struts. Complete geometry in Figure 1d was meshed.

Appendix C: Additional Visuals

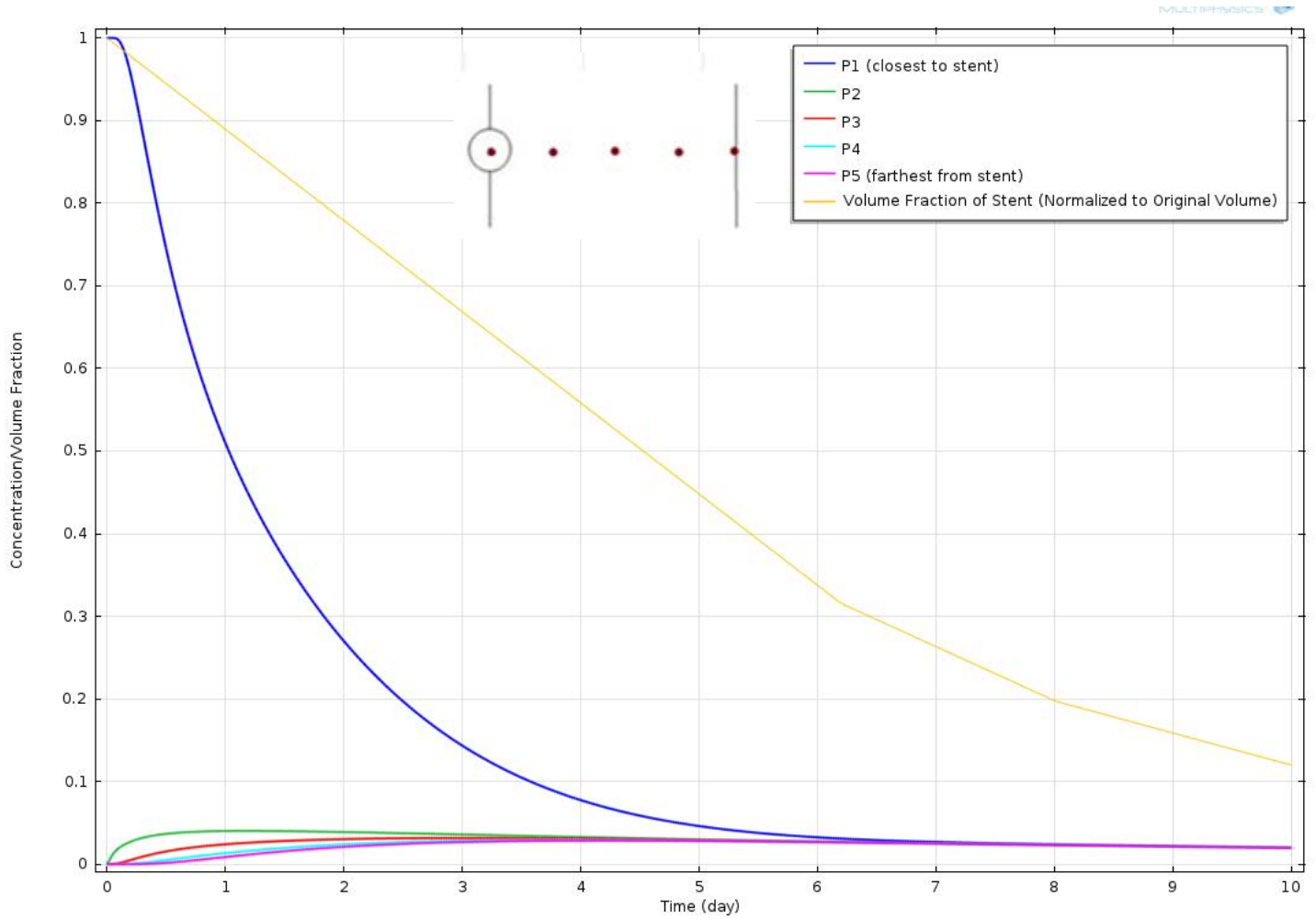


Figure 16: Concentration fractions at different depths and volume fraction of stent with time in degrading model. The concentration in the middle of the stent (P1) converges with the concentrations in the colon before the time the stent takes to degrade to 10% of its original volume.

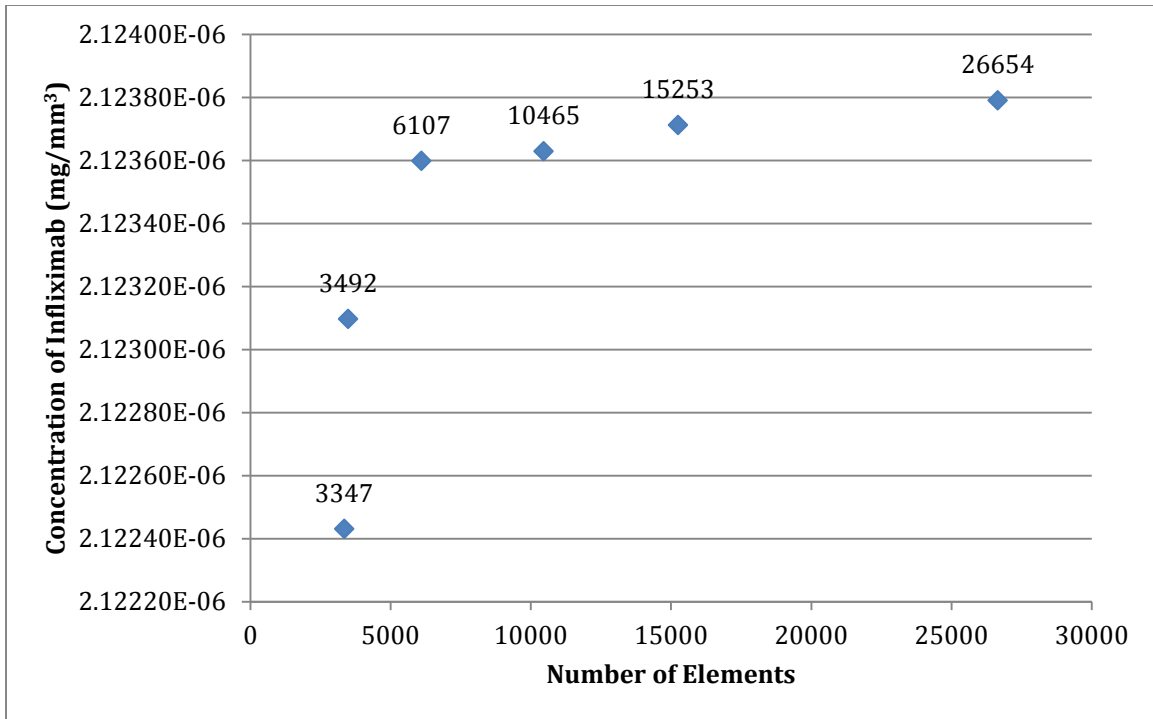


Figure 17: Mesh convergence at 126000 seconds. Convergence is achieved with 15253 elements.

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